

P/ NT COOPERATION TREAT

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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year) 22 February 2001 (22.02.01)	
International application No. PCT/US00/14351	Applicant's or agent's file reference 150.194WO1
International filing date (day/month/year) 24 May 2000 (24.05.00)	Priority date (day/month/year) 24 May 1999 (24.05.99)
Applicant SIMARI, Robert	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
19 December 2000 (19.12.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

S. Mafla



REC'D 14 SEP 2001

WIPO

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 150.194WO1	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/14351	International filing date (day/month/year) 24/05/2000	Priority date (day/month/year) 24/05/1999
International Patent Classification (IPC) or national classification and IPC A61K48/00		
Applicant MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 9 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input checked="" type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 		
Date of submission of the demand 19/12/2000	Date of completion of this report 12.09.2001	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Brenz Verca, S Telephone No. +49 89 2399 7702 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/14351

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-60 as originally filed

Claims, No.:

1-46 as originally filed

Drawings, sheets:

1/10-10/10 as originally filed

Sequence listing part of the description, pages:

1-8, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/14351

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-30 with regard to industrial applicability.

because:

- ☒ the said international application, or the said claims Nos. 1-30 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/14351

- ☐ restricted the claims.
 - ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ neither restricted nor paid additional fees.
2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
- ☒ all parts.
 - ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4, 6-16, 19-20, 24-29, 31-40, 42-46
	No:	Claims	5, 17, 18, 21, 22, 23, 30, 41
Inventive step (IS)	Yes:	Claims	none
	No:	Claims	1-46
Industrial applicability (IA)	Yes:	Claims	31-46
	No:	Claims	

2. Citations and explanations **see separate sheet**

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Section III (Non- establishment of opinion)

Claims 1-30 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section IV (Lack of unity of invention)

Reference is made to the following documents:

- D1:** WO 99 12576 A (CHAO JULIE ;CHAO LEE (US); MUSC FOUNDATION FOR RESEARCH D (US)) 18 March 1999 (1999-03-18)
- D2:** LIN KF, CHAO J AND CHAO L: 'Atrial natriuretic peptide gene delivery attenuates hypertension, cardiac hypertrophy and renal injury in salt-sensitive rats', HUMAN GENE THERAPY, , 01. July 1998, vol. 9, no. 10, pages 1429 to 1438.

The present application does not fulfill the requirement of unity of the invention (Rule 13.1 PCT). The separate inventions/groups of invention are:

1. Claims 1, 3, 4, 11, 13, 15, 25, 26, 32, 36, 37, 42 (entirely)
Claims 2, 5, 17-23, 27-30, 34, 35, 38-40, 44-46 (partially)

Method to inhibit or prevent heart failure, hypertension, vasospasm, atherosclerosis, to relax cardiac muscle, to increase brain natriuretic peptide levels comprising administering an effective amount of a composition comprising a nucleic acid segment encoding brain natriuretic peptide (BNP) or a chimera thereof in a delivery vehicle.

Method to detect progression of heart failure in a mammal subjected to BNP gene therapy. Viral vectors expressing BNP or a chimera thereof.

2. Claims 6-10, 12, 14, 16, 24, 31, 33, 41 (entirely)
Claims 2, 5, 17-23, 27-30, 34, 35, 38-40, 44-46 (partially)

Method to inhibit or prevent heart failure, hypertension, vasospasm, atherosclerosis, to relax cardiac muscle, to increase D-type natriuretic peptide levels comprising

administering an effective amount of a composition comprising a nucleic acid segment encoding dendroaspis natriuretic peptide (DNP) or a chimera thereof in a delivery vehicle.

Method to detect progression of heart failure in a mammal subjected to DNP gene therapy. Viral vectors and plasmids expressing DNP or a chimera thereof.

The single general inventive concept (Rule 13.1 PCT) common to both invention is gene therapy using natriuretic peptides for the treatment of cardiovascular disorders. However this concept is not novel because the use of a natriuretic peptide (ANP) in this kind of gene therapy is disclosed in D1 and also in D2 (see whole documents).

Section V (Reasoned statement)

In addition to the documents mentioned under IV, reference is made to the following documents:

- D3:** LIN KF, CHAO J AND CHAO L: 'Human atrial natriuretic peptide gene delivery reduces blood pressure in hypertensive rats.', HYPERTENSION, December 1995, vol. 26, no. 6, pages 847 to 853.
- D4:** VLASUK GP ET AL: 'Expression and secretion of biologically active human atrial natriuretic peptide in *Saccharomyces cerevisiae*', JOURNAL OF BIOLOGICAL CHEMISTRY, 15. April 1986, vol. 261, no. 11, pages 4789 to 4796.
- D5:** NIKOLAIDIS MN ET AL: 'Synthesis and secretion of human atrial natriuretic factor in *Escherichia coli* cells', MOL BIOL (MOSK), September/October 1994, vol. 28, no. 5, pages 1098 to 1105.
- D6:** STEIN BRUCE C ET AL: 'Natriuretic peptides: Physiology, therapeutic potential, and risk stratification on ischemic heart disease.' AMERICAN HEART JOURNAL, vol. 135, no. 5 PART 1, May 1998 (1998-05), pages 914-923, ISSN: 0002-8703
- D7:** EP-A-0 911 034 (SUNTORY LTD) 28 April 1999 (1999-04-28).
- D8:** SCHIRGER JOHN A ET AL: 'Antiproliferative and vasodilating actions of BNP: Modulation by atherosclerosis and NEP inhibition.' CIRCULATION, vol. 98, no. 17 SUPPL., 27 October 1998 (1998-10-27), pages I598-I599, 71st Scientific Sessions of the American Heart Association; Dallas, Texas, USA; November 8-11, 1998 ISSN: 0009-7322
- D9:** SCHIRGER JOHN A ET AL: 'Presence of Dendroaspis natriuretic peptide-like

immunoreactivity in human plasma and its increase during human heart failure.' MAYO CLINIC PROCEEDINGS, vol. 74, no. 2, February 1999 (1999-02), pages 126-130, ISSN: 0025-6196 cited in the application

1. Novelty

- 1.1 With regard to novelty, prior art D2 (see entire document) discloses the use of an adenovirus expressing atrial natriuretic peptide (ANP) as gene delivery vehicle into rats, where systemic delivery of this vector caused significant reduction in blood pressure. This disclosure is therefore prejudicial to claim 5 and its dependent claims 17, 18, 21 and 30.
- 1.2 Prior art D3 (see entire document) further discloses the use of naked plasmid DNA for ANP gene delivery to rats, inducing a decrease in blood pressure. Consequently, the subject matter of claims 22 and 23, which are dependent claims of claim 5, is also not novel.
- 1.3 D4 and D5 (see abstracts) both disclose chimeric natriuretic peptides comprising at least a portion of DNP, as claimed in 41. Since the length of this portions is not specified, single amino acids or short stretches of DNP which are in common with ANP or any amino acid of the fusion partner in D4 or D5 can be considered as "portions of DNP". This novelty objection is the result of a lack of clarity (see under VIII) and affects claim 41.
- 1.4 The remaining claims 1-4, 6-16, 19-20, 24-29, 31-40 and 42-46 are novel.

2. Inventive step

- 2.1 D1 or D2 can be regarded as the closest prior art. Both of them disclose methods and compositions for the treatment of cardiac disorders involving gene transfer for atrial natriuretic peptide (ANP) expression in vivo. The difference is that the present invention uses brain natriuretic peptide (BNP) or dendroaspis natriuretic peptide (DNP). In the light of this prior art the problem to be solved by the invention has thus to be seen as how to provide alternative methods and composition for gene therapy of cardiovascular disorders.

D6 (entire document) deals with various types of natriuretic peptides, including brain natriuretic peptide (BNP), and their therapeutic potential. D7 (entire document) discloses medicinal compositions including BNP and their use for treating cardiac diseases. D8 describes the vasodilating action of BNP. D9 refers to vasorelaxing properties of DNP and explicitly states that DNP, like ANP and BNP, may have

therapeutic efficacy in human heart failure.

It would be obvious for the person skilled in the field to combine the teaching of the closest prior art with the teaching from the other prior art documents in order to solve the problem of the invention, thus providing vectors expressing BNP or DNP, which are valuable alternatives to ANP.

The construction of chimeras is a common place in the art. The use of alternative viral vectors (AAV) is matter of usual design procedure in gene therapy. The particular embodiments of the dependent claims also do not add any technical feature which would make the subject matter inventive over the matter claimed in the independent claims.

Consequently, no inventive step is acknowledged for all claimed matter (Article 33(3) PCT).

3. Industrial applicability

- 3.1 For the assessment of the present claims 1-30 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
- 3.2 The subject matter of claims 31-46 fulfill the requirements of industrial application (Article 33(4) PCT).

Section VIII (Certain observations on the international application)

The following observations are made under Article 6 PCT:

- 1.1 The term "chimera" or "chimera thereof" in all concerned claims is vague and open to interpretation. To make a chimera at least two partners are necessary, however in the concerned claims this term always refers singularly either to BNP or to DNP. Beside any unspecified portion(s) of BNP or DNP, the skilled person does not know what kind of fusion partners participate in building the claimed chimera and to which extent each partner participates. This unclarity engenders a problem of novelty (see

under III 1.3), since in an extreme case a single amino acid could be seen as a portion of one fusion partner in a chimera.

- 1.2 Dependent claims 30 and 34 add a technical feature (promoter) which is of course essential for the invention and which the examiner assumed to be implicitly present in the independent claims referred to, i.e. due to the formulation using the term "comprising". It is otherwise unclear how an effective gene expression shall be achieved in absence of a promoter. It is thus not clear why this specific embodiment is needed.
- 1.4 The terms "purified" in claim 41 is a relative term which is open to interpretation.

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REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 150.194WO1

Box No. I TITLE OF INVENTION

ADENOVIRUS VECTORS ENCODING BRAIN NATRIURETIC PEPTIDE

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH
200 First Street SW
Rochester, Minnesota 55905
United States of America

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

This person is applicant for the purposes of:

☐ all designated States

☒ all designated States except the United States of America

☐ the United States of America only

☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

SIMARI, Robert
200 First Street SW
Rochester, Minnesota 55905
United States of America

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

This person is applicant for the purposes of:

☒ all designated States

☐ all designated States except the United States of America

☐ the United States of America only

☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent

☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

VIKSNINS, Ann S.
Schwegman, Lundberg, Woessner & Kluth
P.O. Box 2938
Minneapolis, Minnesota 55402
United States of America

Telephone No.

(612) 373-6900

Facsimile No.

(612) 339-3061

Teleprinter No.

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):


Regional Patent

- ☒ **AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|---|--|
| <input checked="" type="checkbox"/> AE United Arab Emirates | <input checked="" type="checkbox"/> LR Liberia |
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LS Lesotho |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> LT Lithuania |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> MA Morocco |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BR Brazil | |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> MW Malawi |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> MX Mexico |
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| <input checked="" type="checkbox"/> CR Costa Rica | <input checked="" type="checkbox"/> NZ New Zealand |
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| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> RU Russian Federation |
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| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> GD Grenada | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> GE Georgia | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> GH Ghana | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> TZ United Republic of Tanzania |
| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> IN India | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> IS Iceland | |
| <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | <input checked="" type="checkbox"/> ZA South Africa |
| | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> KR Republic of Korea | Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet: |
| <input checked="" type="checkbox"/> KZ Kazakhstan | <input checked="" type="checkbox"/> AG Antigua and Barbuda |
| <input checked="" type="checkbox"/> LC Saint Lucia | <input checked="" type="checkbox"/> DZ Algeria |
| <input checked="" type="checkbox"/> LK Sri Lanka | |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) (24.05.99) 24 May 1999	60/135,490	US		
item (2)				
item (3)				
<input checked="" type="checkbox"/> The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (1)				
<small>* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.</small>				
Box No. VII INTERNATIONAL SEARCHING AUTHORITY				
Choice of International Searching Authority (ISA) <small>(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):</small> ISA / EP		Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority): Date (day/month/year) Number Country (or regional Office)		
Box No. VIII CHECK LIST; LANGUAGE OF FILING				
This international application contains the following number of sheets: request : 3 description (excluding sequence listing part) : 60 claims : 6 abstract : 1 drawings : 8 sequence listing part of description : 8 Total number of sheets : 86		This international application is accompanied by the item(s) marked below: 1. <input checked="" type="checkbox"/> fee calculation sheet 2. <input type="checkbox"/> separate signed power of attorney 3. <input checked="" type="checkbox"/> copy of general power of attorney; reference number, if any: 4. <input type="checkbox"/> statement explaining lack of signature 5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): 6. <input type="checkbox"/> translation of international application into (language): 7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material 8. <input checked="" type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form 9. <input checked="" type="checkbox"/> other (specify): general transmittal; return postcard; Comm. re: sequence listing		
Figure of the drawings which should accompany the abstract: 8		Language of filing of the international application: English		
Box No. IX SIGNATURE OF APPLICANT OR AGENT				
<small>Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).</small>				
 Ann S. Viksnins				

For receiving Office use only	
1. Date of actual receipt of the purported international application: JC18 Rec'd PCT/PTO 1.5 NOV 2001	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.

For International Bureau use only
Date of receipt of the record copy by the International Bureau:

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 150.194W01	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 00/14351	International filing date (day/month/year) 24/05/2000	(Earliest) Priority Date (day/month/year) 24/05/1999
Applicant MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:
- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

- ☐ the text is approved as submitted by the applicant.
- ☒ the text has been established by this Authority to read as follows:

ADENOVIRUS VECTORS ENCODING BRAIN NATRIURETIC PEPTIDE

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

- ☐ as suggested by the applicant.
- ☐ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.
- ☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 00/14351

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K48/00 C12N15/16 A61P9/04 A61P9/10 A61P9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, MEDLINE, CHEM ABS Data, EMBASE, WPI Data, EPO-Internal, STRAND

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 12576 A (CHAO JULIE ; CHAO LEE (US); MUSC FOUNDATION FOR RESEARCH D (US)) 18 March 1999 (1999-03-18) the whole document	1-46
Y	STEIN BRUCE C ET AL: "Natriuretic peptides: Physiology, therapeutic potential, and risk stratification on ischemic heart disease." AMERICAN HEART JOURNAL, vol. 135, no. 5 PART 1, May 1998 (1998-05), pages 914-923, XP000960390 ISSN: 0002-8703 the whole document	1-46

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

8 November 2000

Date of mailing of the international search report

20/11/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 eponl,
Fax: (+31-70) 340-3016

Authorized officer

Niemann, F

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 911 034 A (SUNTORY LTD) 28 April 1999 (1999-04-28) abstract page 2, line 1 - line 51 claims 1-3,5 ---	1-5, 11, 17-23, 25, 26, 28-30, 32, 34-40, 42, 44-46
Y	EP 0 533 084 A (SCHERING CORP) 24 March 1993 (1993-03-24) abstract page 2, line 1 -page 3, line 15; claims 1,2 ---	13, 15, 17-23, 25, 26, 28-30, 32, 34-40, 42, 44-46
Y	SCHIRGER JOHN A ET AL: "Antiproliferative and vasodilating actions of BNP: Modulation by atherosclerosis and NEP inhibition." CIRCULATION, vol. 98, no. 17 SUPPL., 27 October 1998 (1998-10-27), pages I598-I599, XP000960360 71st Scientific Sessions of the American Heart Association; Dallas, Texas, USA; November 8-11, 1998 ISSN: 0009-7322 the whole document ---	13, 15, 17-23, 25, 26, 28-30, 32, 34-40, 42, 44-46
Y	SCHIRGER JOHN A ET AL: "Presence of Dendroaspis natriuretic peptide-like immunoreactivity in human plasma and its increase during human heart failure." MAYO CLINIC PROCEEDINGS, vol. 74, no. 2, February 1999 (1999-02), pages 126-130, XP000960384 ISSN: 0025-6196 cited in the application the whole document --- -/--	6-10, 12, 14, 16, 24, 31, 33, 41, 43

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	<p>KANTOR BIRGIT ET AL: "Systemic and myocardial expression of brain natriuretic peptide after adenoviral-mediated gene transfer using a new catheter-based approach." JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY., vol. 35, no. 2 suppl. A, February 2000 (2000-02), page 234A XP000960380 29th Annual Scientific Session of the American College of Cardiology.;Anaheim, California, USA; March 12-15, 2000 ISSN: 0735-1097 the whole document</p>	<p>1-5,11, 17-23, 25,26, 28-30, 32, 34-40, 42,44-46</p>

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1, 3,4, 11,13, 15,25,26,32,36,37,
42 and partially 2,5,17-23,28-30,34,35,38-40,44-46

method to inhibit or prevent heart failure, hypertension, vasospasm, atherosclerosis, to relax cardiac muscle, to increase brain natriuretic peptide levels, comprising administering to the mammal an effective amount of a composition comprising a nucleic acid segment encoding brain natriuretic peptide or a chimera thereof in a delivery vehicle.

method to detect progression of heart failure in a mammal subjected to brain natriuretic gene therapy

2. Claims: 6-10, 12,14, 16, 24,27,31,33,41,
43 and partially 2,5,17-23,28-30,34,35,38-40,44-46

method to inhibit or prevent heart failure, hypertension, vasospasm, atherosclerosis, to relax cardiac muscle, to increase brain natriuretic peptide levels, comprising administering to the mammal an effective amount of a composition comprising a nucleic acid segment encoding D-type natriuretic peptide or a chimera thereof in a delivery vehicle.

method to detect progression of heart failure in a mammal subjected to D-type natriuretic gene therapy

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim(s) 4, 10 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 1-3, 5-9, 11-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/14351

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/US 00/14351

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9912576 A	18-03-1999	AU 9487698 A	29-03-1999
EP 0911034 A	28-04-1999	AU 5780398 A	26-08-1998
		CA 2251155 A	13-08-1998
		CN 1219134 A	09-06-1999
		CN 1219134 T	09-06-1999
		WO 9834636 A	13-08-1998
EP 0533084 A	24-03-1993	AU 2650692 A	27-04-1993
		CA 2119019 A	01-04-1993
		EP 0605589 A	13-07-1994
		JP 6510787 T	01-12-1994
		MX 9205274 A	30-06-1994
		WO 9305809 A	01-04-1993

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
30 November 2000 (30.11.2000)

PCT

(10) International Publication Number
WO 00/71576 A3

(51) International Patent Classification⁷: A61K 48/00,
C12N 15/16, A61P 9/04, 9/10, 9/12

(21) International Application Number: PCT/US00/14351

(22) International Filing Date: 24 May 2000 (24.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/135,490 24 May 1999 (24.05.1999) US

(71) Applicant (for all designated States except US): MAYO
FOUNDATION FOR MEDICAL EDUCATION AND
RESEARCH [US/US]; 200 First Street SW, Rochester,
MN 55905 (US).

(71) Applicant and

(72) Inventor: SIMARI, Robert [US/US]; 200 First Street SW,
Rochester, MN 55905 (US).

(74) Agent: VIKSNINS, Ann, S.; Schwegman, Lundberg,
Woessner & Kluth, P.O. Box 2938, Minneapolis, MN
55402 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE,
DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- With international search report.
- Before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments.

(88) Date of publication of the international search report:
25 January 2001

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: ADENOVIRUS VECTORS ENCODING BRAIN NATRIURETIC PEPTIDE

(57) Abstract: The invention provides isolated and purified nucleic acid molecules encoding a natriuretic peptide useful in methods to inhibit or prevent heart failure.

WO 00/71576 A3

From the INTERNATIONAL SEARCHING AUTHORITY

PCTNOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To:

Schwegman, Lundberg, Woessner
& Kluth
Attn. VIKSNINS, A.
P.O.Box 2938
Minneapolis, Minnesota 55402
UNITED STATES OF AMERICADate of mailing
(day/month/year)

20/11/2000

Applicant's or agent's file reference

150.194W01

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US 00/14351

International filing date
(day/month/year)

24/05/2000

Applicant

MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH

- 1.
- ☒
- The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.**Where?** Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35**For more detailed instructions,** see the notes on the accompanying sheet.

- 2.
- ☐
- The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

- 3.
- ☐
- With regard to the protest**
- against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

- 4.
- Further action(s):**
- The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority

European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Catherine Humbert

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 150.194W01	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 00/ 14351	International filing date (day/month/year) 24/05/2000	(Earliest) Priority Date (day/month/year) 24/05/1999
Applicant MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

ADENOVIRUS VECTORS ENCODING BRAIN NATRIURETIC PEPTIDE

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K48/00 C12N15/16 A61P9/04 A61P9/10 A61P9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, MEDLINE, CHEM ABS Data, EMBASE, WPI Data, EPO-Internal, STRAND

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 12576 A (CHAO JULIE ;CHAO LEE (US); MUSC FOUNDATION FOR RESEARCH D (US)) 18 March 1999 (1999-03-18) the whole document	1-46
Y	STEIN BRUCE C ET AL: "Natriuretic peptides: Physiology, therapeutic potential, and risk stratification on ischemic heart disease." AMERICAN HEART JOURNAL, vol. 135, no. 5 PART 1, May 1998 (1998-05), pages 914-923, XP000960390 ISSN: 0002-8703 the whole document	1-46

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *8* document member of the same patent family

Date of the actual completion of the international search

8 November 2000

Date of mailing of the international search report

20/11/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Niemann, F

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 911 034 A (SUNTORY LTD) 28 April 1999 (1999-04-28) abstract page 2, line 1 - line 51 claims 1-3,5 ---	1-5, 11, 17-23, 25, 26, 28-30, 32, 34-40, 42, 44-46
Y	EP 0 533 084 A (SCHERING CORP) 24 March 1993 (1993-03-24) abstract page 2, line 1 -page 3, line 15; claims 1,2 ---	13, 15, 17-23, 25, 26, 28-30, 32, 34-40, 42, 44-46
Y	SCHIRGER JOHN A ET AL: "Antiproliferative and vasodilating actions of BNP: Modulation by atherosclerosis and NEP inhibition." CIRCULATION, vol. 98, no. 17 SUPPL., 27 October 1998 (1998-10-27), pages I598-I599, XP000960360 71st Scientific Sessions of the American Heart Association; Dallas, Texas, USA; November 8-11, 1998 ISSN: 0009-7322 the whole document ---	13, 15, 17-23, 25, 26, 28-30, 32, 34-40, 42, 44-46
Y	SCHIRGER JOHN A ET AL: "Presence of Dendroaspis natriuretic peptide-like immunoreactivity in human plasma and its increase during human heart failure." MAYO CLINIC PROCEEDINGS, vol. 74, no. 2, February 1999 (1999-02), pages 126-130, XP000960384 ISSN: 0025-6196 cited in the application the whole document --- -/--	6-10, 12, 14, 16, 24, 31, 33, 41, 43

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	<p>KANTOR BIRGIT ET AL: "Systemic and myocardial expression of brain natriuretic peptide after adenoviral-mediated gene transfer using a new catheter-based approach."</p> <p>JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY., vol. 35, no. 2 suppl. A, February 2000 (2000-02), page 234A XP000960380 29th Annual Scientific Session of the American College of Cardiology.;Anaheim, California, USA; March 12-15, 2000 ISSN: 0735-1097 the whole document -----</p>	<p>1-5,11, 17-23, 25,26, 28-30, 32, 34-40, 42,44-46</p>

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1, 3,4, 11,13, 15,25,26,32,36,37,
42 and partially 2,5,17-23,28-30,34,35,38-40,44-46

method to inhibit or prevent heart failure, hypertension, vasospasm, atherosclerosis, to relax cardiac muscle, to increase brain natriuretic peptide levels, comprising administering to the mammal an effective amount of a composition comprising a nucleic acid segment encoding brain natriuretic peptide or a chimera thereof in a delivery vehicle.

method to detect progression of heart failure in a mammal subjected to brain natriuretic gene therapy

2. Claims: 6-10, 12,14, 16, 24,27,31,33,41,
43 and partially 2,5,17-23,28-30,34,35,38-40,44-46

method to inhibit or prevent heart failure, hypertension, vasospasm, atherosclerosis, to relax cardiac muscle, to increase brain natriuretic peptide levels, comprising administering to the mammal an effective amount of a composition comprising a nucleic acid segment encoding D-type natriuretic peptide or a chimera thereof in a delivery vehicle.

method to detect progression of heart failure in a mammal subjected to D-type natriuretic gene therapy

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim(s) 4, 10 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 1-3, 5-9, 11-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/14351

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9912576	A	18-03-1999	AU 9487698 A	29-03-1999
EP 0911034	A	28-04-1999	AU 5780398 A	26-08-1998
			CA 2251155 A	13-08-1998
			CN 1219134 A	09-06-1999
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			WO 9834636 A	13-08-1998
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			MX 9205274 A	30-06-1994
			WO 9305809 A	01-04-1993

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/14351

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.